45. (New) The G-protein fusion receptor of claim 1, wherein said intracellular domain has at least 90% sequence identity with a portion of a MRluR intracellular domain sequence at least 50 amino acids in length.

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46. (New) The G-protein fusion receptor of claim 1, wherein said intracellular domain has at least 90% sequence identity with a portion of a $GABA_B$ receptor intracellular domain sequence at least 50 amino acids in length.

Remarks

The present claims concern fusion receptors that include a G-protein linked to the intracellular domain derived from a CaR, mGluR, or $GABA_B$ receptor.

Claim 1 is amended to expressly indicate that the intracellular domain in the G-protein fusion receptor is not linked to a G-protein with which it interacts in a wild type receptor. Support for this amendment is provided in the specification, for example, at p.13, lines 4-11. Claim 5 is amended to insert the proper Greek letter alpha. Support is provided in the parent PCT application. The reference to "fusion receptor" in each of claims 6-9 corrects the reference to a term in antecedent claims, and support is provided, for example, by antecedent claims 1-5. Amendment of claim 6 to refer to $GABA_B$ receptor in place of mGluR corrects an obvious typographical error and is consistent with the specification. New claims 42 and 43 replace the multiple dependency from prior claim 5. Support for new claims 44-46 is provided, for example, on p.14, line 5 and p.3, line 15. Thus, no new matter is added by the amendments.

Objection to the Oath/Declaration

A substitute Declaration is submitted herewith, correcting items noted by the Examiner.

Objections to the Specification

A. In response to the Examiner's instruction, the title has been amended to conform to the claims under consideration.

B & E. A substitute specification is submitted without punched holes and with missing symbols inserted. The missing symbols represent obvious typographic errors and were present in the parent PCT application, and therefore do not represent new matter.

D. Formal drawings are submitted herewith.

Objections to the Claims

A. The Examiner objected to the syntax of claim 1 and suggested the insertion of a colon after "comprising". Applicant respectfully submits that insertion of a colon after "comprising" is undesirable as it would inappropriately introduce a break in the sentence structure of the claim. Thus, Applicant requests that the Examiner reconsider and withdraw this objection. While Applicant submits that claim 1 was appropriate without insertion of the letter identifiers suggested by the Examiner, in order to facilitate prosecution, claim 1 is amended to insert those identifiers.

B & C. Claim 5 was amended to insert the missing period, and claims 7, 8, and 11 were amended to insert "or" as suggested by the Examiner.

Rejections under 35 USC § 112, first paragraph

The Examiner rejected claims 1-11 under 35 USC § 112, first paragraph as allegedly not being enabled. The Examiner recognized that the disclosure was enabling for a G-protein fusion receptor that includes domains from CaR, mGluR, and/or $GABA_B$ receptor, but asserted that the disclosure did not enable receptors that included domains "substantially similar" to CaR, mGluR, and/or $GABA_B$ receptor domains, or in which the intracellular domain comprises "at least about 10 amino acids" from the intracellular domain of a CaR, mGluR, or $GABA_B$ receptor. The Examiner alleged that undue experimentation would be required to practice the claimed invention. Applicant respectfully traverses these rejections.

One of ordinary skill in the art will recognize, based on amino acid sequence differences between CaR, mGluR, and $GABA_B$ receptors from different sources, that the various domains of these receptors and thus of the claimed fusion receptors can encompass such variations and remain functional. Such a person of ordinary skill is also familiar with standard techniques for

providing polypeptides with a desired amino acid sequence. The present disclosure provides examples of G-protein fusion receptors as claimed. Thus, using the guidance provided by the present disclosure, such a person could construct fusion receptors, express the receptors in suitable cells, and assay for receptor signal transduction.

Likewise, intracellular domains that include at least 10 amino acids substantially similar to an intracellular domain of a CaR, mGluR, or $GABA_B$ receptor can be readily constructed as indicated above, included in a fusion receptor, and the fusion receptor tested for signal transduction.

Therefore, Applicant submits that no undue experimentation would be involved in this process, and respectfully requests that the Examiner reconsider and withdraw this rejection.

Rejections under 35 USC § 112, second paragraph

A. The Examiner asserted that claim 5 was unclear due to apparently missing Greek alpha. As indicated above, claim 5 was amended to insert the Greek symbols.

B. In response to the Examiner's objection, claim 6 was amended to correct the typographical error by replacing the final "mGluR" with "$GABA_B$".

C. With respect to the Examiner's assertion that the term "nucleic acid" in claim 10 lacked sufficient antecedent basis, claim 10 was amended to expressly state that the "vector" comprises the "nucleic acid".

D. Also with respect to claim 10, the Examiner asserted that claim 10 was unclear because it was not clear what elements are being used for introducing a heterologous nucleic acid into the claimed cell. Applicant respectfully traverses this rejection. As is indicated in the Specification at p.19, lines 3-7, a variety of different techniques can be used to transfect a cell with the specified vectors. One of ordinary skill in the art recognizes that different methods utilize different "elements", and further recognizes suitable "elements" for the different techniques. Indeed, examples of transfection are provided in Examples 2-4, utilizing injection (Examples 2 and 3) or Gibco BRL Life Technologies' Lipofectamine reagent. Thus, these Examples provide exemplary techniques and elements. Thus, Applicant respectfully submits that claim 10 is appropriately clear.

E. The Examiner rejected claim 11, asserting that the claim was incomplete for omitting essential steps, i.e., the step of recovering the fusion protein from the culture. Applicant respectfully traverses this rejection. Contrary to the Examiner's assertion, purified fusion protein is not the only form that can usefully be produced. For example, at p.18, lines 16-21, the specification points out that transfected cell lines expressing fusion receptors can be used for high-throughput screening, for assay binding, and as factories to produce large amounts of a receptor. Clearly, the first two of the described uses do not involve purification of receptor from culture. Thus, it is not necessary or even appropriate to insert a step of recovering the fusion protein from the culture in claim 11.

In view of the amendments and remarks above, Applicant requests that the Examiner reconsider and withdraw the rejections under 35 USC § 112, second paragraph.

Rejections under 35 USC § 103

The Examiner rejected claims 1-11 under 35 USC § 103(a) as allegedly being unpatentable over Fuller et al. (reference A6), in view of Bertin et al. (reference A27), further in view of Negulescu et al. (reference A20), further in view of Kaupmann et al. (reference A11), and further in view of Rock et al. (Vaccine 14:1560-1568, 1996). Applicant respectfully traverses these rejections.

The Examiner asserted that the artisan would have had a reasonable expectation of success in producing the claimed fusion receptors since the DNA for all the human receptors was know and the technology to produce fusion proteins was well-known and highly successful in the art at the time of the invention.

First, Applicant notes that present claim 1 was amended to expressly indicate that the G-protein joined to the intracellular domain of the fusion receptor is different from one that interacts with that intracellular domain in a wild type receptor. Thus, the signal activated by the receptor can be changed as compared to the wild type.

Applicant also notes that the Examiner has not shown, based on evidence from the art, that the creation of the claimed fusion receptors would have been obvious to try, but instead asserts that the artisan would have had a reasonable expectation of success, and that it would

have been obvious to perform certain actions. The question of whether there would have been a reasonable expectation of success can only arise if it would have been obvious to try the claimed fusion receptors. In this case, Applicant submits that it would not have been obvious to try these receptors, as there is no suggestion from the art to combine the references in the manner indicated by the Examiner to lead to the present invention. The requirement for such motivation or suggestion to combine references has been a consistent holding by the Federal Circuit.

In addition, nothing cited by the Examiner suggests a fusion between an intracellular domain derived from a CaR, mGluR or $GABA_B$ receptor and a G-protein that would not interact with that intracellular domain in a wild type receptor (as specified in Claim 1 as amended). To the contrary, the only fusion receptor cited involved a fusion between a wild type receptor and a $G_s\alpha$ with which the receptor normally interacts. (Bertin et al. (1994) PNAS 91:8827-8831.) There is no indication that a fusion should be made with a CaR, mGluR, or $GABA_B$ receptor intracellular domain. To the contrary, the apparent primary purpose of making the fusion was to elucidate the interactions between the members of the signaling pathway. Such a purpose seems incompatible with the substitution suggested by the Examiner.

Further, as part of the assertion of obviousness, the Examiner cites Bertin et al. for the proposition that "precoupling a receptor to a G-protein subunit by a physical link might focus the receptor-mediated signal toward a more potent and/or more selective targeting of a single cellular effector (citing p.8827, left column, last paragraph). However, that citation referred to precoupling to a naturally interacting G-protein subunit. It provides no indication that such an effect could be obtained using G-proteins of a type that do not normally interact with that receptor intracellular domain, or even that such precoupling would give those effects with CaR, mGluR, or $GABA_B$ receptor intracellular domains.

In addition, though the Examiner asserted that Fuller et al. describes fusion receptors, the receptors described therein are more properly referred to as chimeric receptors, as they include domains from different receptors. Likewise, the $GABA_B$ receptors described by Kaupmann et al. are not fusion receptors as in the present claims. Indeed, the Examiner admitted that neither Fuller nor Kaupmann describe fusion receptors that include a G-protein.

The Negulescu et al. reference cited by the Examiner also does not provide the suggestion to combine the cited references to produce the present invention. Negulescu et al. describes the expression of promiscuous G-proteins in cells and detection of activation of undefined "G-protein coupled receptors". (See, e.g., Examples 4-8.) This did not include construction of fusion receptors. Since there is no suggestion from the cited references to create the claimed fusion receptors, Negulescu et al. reference cannot suggest the claimed invention.

Further, while the Examiner has asserted that it would have been obvious to utilize a linker between the intracellular domain and a G-protein, Applicant respectfully submits that this represent improper use of hindsight in view of Applicant's disclosure. The only reference cited by the Examiner that concerned a receptor fused to a G-protein component (Bertin et al.) did not describe or suggest use of a linker. The reference cited by the Examiner in connection with linkers (Rock et al., *Vaccine* 14:1560-1568, 1996) does not concern fusion receptors or even receptors. Instead, the reference concerns the immunogenicity of the beta subunit carboxyl terminal peptide of human chorionic gonadotripin when fused through a linker to the B subunit of *E. coli* heat-labile enterotoxin (LTB). This was done in connection with prior work relating to raising specific immune responses against numerous antigens linked as fusion protein linked to LTB. (Rock, p.1561, column 1), for the purpose of developing an improved hCG vaccine formulation (*Id.*, p.1564, column 1). Applicant submits that there is no reasonable relationship between using a linker in an immunogenic construct and using a linker in a fusion receptor, so that the Rock et al. reference does not suggest the use of linkers in the present fusion receptors.

In view of the absence of suggestion to construct the present claimed fusion receptors, Applicant respectfully requests that the Examiner reconsider and withdraw these rejections.

Applicant submits that the application is in condition for allowance and respectfully requests a notice to that effect.

If a telephonic discussion would be beneficial to the prosecution of this application, the Examiner is invited to contact the undersigned by telephone at the number provided below.

A request for a 1-month extension of time and a check for the fee for that extension accompanies this response. No additional fee is believed due in connection with this communication. However, if any additional fee is due, kindly charge the appropriate amount to Deposit Account 50-0872 and referencing Docket No. 072827-1801.

Respectfully submitted,

Date: 11/22/02

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Appendix 1: Marked-up copies of replacement amended claims

1. (Amended) A G-protein fusion receptor comprising

a) an extracellular domain comprising an extracellular domain amino acid sequence substantially similar to either an extracellular CaR amino acid sequence, an extracellular mGluR amino acid sequence, or an extracellular $GABA_B$ receptor amino acid sequence;

b) a transmembrane domain joined to the carboxy terminus of said extracellular domain, said transmembrane domain comprising a transmembrane domain amino acid sequence substantially similar to either a transmembrane CaR amino acid sequence, a transmembrane mGluR amino acid sequence, or a transmembrane $GABA_B$ receptor amino acid sequence;

c) an intracellular domain joined to the carboxy terminus of said transmembrane domain comprising all or a portion of an intracellular amino acid sequence substantially similar to either an intracellular CaR amino acid sequence, an intracellular mGluR amino acid sequence, or an intracellular $GABA_B$ receptor amino acid sequence, provided that said portion is at least [about] 10 amino acids;

d) an optionally present linker joined to the carboxy terminus of said intracellular domain; and

e) a G-protein joined either to said intracellular domain or to said optionally present linker, provided that said G-protein is joined to said optionally present linker when said optionally present linker is present,

wherein said intracellular domain when present in a wild type receptor does not interact with said G-protein.

2. The G-protein fusion receptor of claim 1, wherein said extracellular domain consists of said extracellular domain amino acid sequence, said transmembrane domain consists of said transmembrane domain amino acid sequence; and said intracellular domain consists of said transmembrane domain amino acid sequence.

3. The G-protein fusion receptor of claim 2, wherein said optionally present linker is present and is a polypeptide 3 to 30 amino acids in length.

4. The G-protein fusion receptor of claim 2, wherein said optionally present linker is not present.

5. [1.] (Amended) The G-protein fusion receptor of claim 3 [or 4], wherein said G-protein is selected from the group consisting of: $G_{\alpha 15}$, $G_{\alpha 16}$ [G_{15}, G_{16}], Gqo5, and Gqi5.

6. (Amended) The G-protein fusion receptor of claim 5, wherein any of said CaR sequence present is a human CaR sequence, any of said mGluR sequence present is from a human mGluR, and any of said $GABA_B$ receptor sequence present is from human [mGluR] $GABA_B$ receptor.

7. (Amended) A nucleic acid comprising a nucleotide sequence encoding for the G-protein fusion receptor of any one of claims 1-6, 42, or 43.

8. (Amended) An expression vector comprising a nucleotide sequence encoding for the G-protein fusion receptor of any one of claims 1-6, 42, or 43 transcriptionally coupled to a promoter.

9. (Amended) A recombinant cell comprising the expression vector of claim 8 and a cell wherein the G-protein fusion receptor is expressed and is functional.

10. (Amended) A recombinant cell produced by combining a vector of claim 8, wherein said vector comprises [comprising] the nucleic acid of claim 7 [9] and elements for introducing heterologous nucleic acid into a cell wherein the G-protein fusion receptor is expressed, and said cell.

11. (Amended) A process for the production of a G-protein fusion receptor comprising:

growing procaryotic or eukaryotic host cells comprising a nucleic acid sequence expressing the G-protein fusion receptor of any one of claims 1-6, 42, or 43, under suitable nutrient conditions allowing for cell growth.

42. (New) The G-protein fusion receptor of claim 4, wherein said G-protein is selected from the group consisting of: $G_{\alpha 15}$, $G_{\alpha 16}$, Gqo5, and Gqi5.

43. (New) The G-protein fusion receptor of claim 42, wherein any of said CaR sequence present is a human CaR sequence, any of said mGluR sequence present is from a human mGluR, and any of said $GABA_B$ receptor sequence present is from human $GABA_B$ receptor.

44. (New) The G-protein fusion receptor of claim 1, wherein said intracellular domain has at least 90% sequence identity with a portion of a CaR intracellular domain sequence at least 50 amino acids in length.

45. (New) The G-protein fusion receptor of claim 1, wherein said intracellular domain has at least 90% sequence identity with a portion of a MRluR intracellular domain sequence at least 50 amino acids in length.

46. (New) The G-protein fusion receptor of claim 1, wherein said intracellular domain has at least 90% sequence identity with a portion of a $GABA_B$ receptor intracellular domain sequence at least 50 amino acids in length.